REMARKS/ARGUMENTS

I. Status of the Prosecution

The first Office Action following the filing of a Request for Continuing Examination was dated January 7th, 2003 and rejected all pending claims. Claims 35-40 were cancelled in the last entered amendment. Claims 1, 6, 9-10, and 31-32 were amended therein. Claims 1-7, 9-10 and 31-34 remain pending in the application. Claims 9-10 are canceled herein. Claims 41-43 are newly added, and claims 1, 31, and 32 are currently amended.

II. The Claims are not Anticipated by Knuth *et al.* Under 35 U.S.C. 102(b)

A. Claims 31-32 and 34 are Novel Compositions.

Claims 9-10, 31-32 and 34 stand rejected under 35 U.S.C. §102(b) as being anticipated by Knuth *et al.* (US 5,057,424). Applicants respectfully traverse the rejection with respect to claims 31-32 and 34. Claims 9 and 10 have been cancelled herein, thus the rejection is moot with respect to these claims.

Claims 31-32 and 34 are directed to a composition in the form of a cell culture comprising *Vanilla planifolia* cells in a culture medium supplemented with an elicitor of vanillin synthesis selected from the group consisting of malic acid, 3,4-dihydroxybenzaldehyde, a combination of malic acid and 3,4-dihydroxybenzaldehyde, and glycosylated lysozyme, wherein, after 15 days in culture, the cell culture produces at least twice as much vanillin, or ten times as much vanillin, as a cell culture after 15 days in culture under equivalent conditions, in a culture medium which was not supplemented with the elicitor. The claims are also directed to cell cultures as above wherein the *Vanilla planifolia* cells are root cells.

The Office Action alleges that Knuth *et al.*, or any reference teaching *Vanilla planifolia* cells, anticipates the claimed invention, regardless of claim limitations referring to

the method by which such cells are treated or prepared, as the cells taught by Knuth *et al.* would be indistinguishable from the claimed cells. The Office Action also cites *In re Thorpe* and alleges it teaches that a product-by-process claim may be properly rejected over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. Applicants note the important aspect of the holding in *Thorpe* is that the end result was indistinguishable from the prior art. Here, the claims themselves provide a simple and straightforward way of distinguishing prior art cell culture compositions: the cultures are supplemented with an elicitor as defined in the claim, and have the ability to produce two or ten times the amount of vanillin as an equivalent culture without supplementation.

The Office Action apparently construed claims 31-32 and 34 as product-by-process claims, and rejected them in accordance with the holding in *Thorpe*. Applicants respectfully submit, however, that claims 31-32 and 34 as currently amended are not product-by-process claims. It is entirely proper for an applicant to claim compositions of cell cultures in the comparative language used – such language is not properly construed as a product by process claim, wherein "an otherwise patentable product. . .resists definition by other than the process by which it is made." *Thorpe*, 777 F.2d at 697.

Unlike the claims at issue in that case, here Applicants have claimed a cell culture composition supplemented with an elicitor, subject to a further limitation of producing comparatively greater amounts of vanillin than a cell culture composition without the elicitor. Such claims are common in biotechnology patents and are not viewed as product-by-process claims. While claims 9 and 10 were directed to cells produced by a particular method, no such limitation can be read into claims 31-32, and 34. Additionally, as Applicants understand it, the Office Action contends that "*regardless* of claim limitations referring to the method by which such cells are treated or prepared" any reference teaching *Vanilla planifolia* cells would anticipate the claims since the cells would be indistinguishable from the claimed cells. This is clearly an improper standard even for product-by-process claims, wherein the *product* could be further limited to distinguish it from the prior art product. Whereas the production of the claimed cells by a particular process would be properly anticipated by cells having the required basic limitations, here, the further limitation relating to the increase in the production of vanillin at day 15 of culture in no way constitutes a limitation "referring to the

method by which such cells are treated or prepared" even if the supplementation treatment were so construed. Rather, this further limitation adds a required characteristic which one skilled in the art would clearly understand, and recognize that the inventors were in possession of such cultures.

The claims as currently amended, therefore, are not anticipated by Knuth *et al.* under proper standards for anticipation –because Knuth *et al.* do not teach each and every limitation of the claimed invention either expressly or inherently. "Anticipation under 35 U.S.C. §102 requires that a single prior art reference teach each and every limitation of the claimed invention." *Moba, B.V. v. Diamond Automation*, 2003 U.S. App LEXIS 6285 (Fed. Cir. 2003) *citing Electro Med. Sys. S.A. v. Cooper Life Sci.*, 34 F.3d 1048, 1052 (Fed. Cir. 1994). In particular, Knuth *et al.* do not teach any cell cultures comprising *Vanilla planifolia* in a culture medium supplemented according to the claims, which produce, at day 15 of culture, two, or ten, times the amount of vanillin as equivalent unsupplemented cell cultures. Knuth *et al.* do **not** teach the claimed supplementation, and more particularly, they do not teach a two- or ten-fold increase in vanillin at day 15 of culture. Thus, when the claims are properly construed, Knuth *et al.* cannot properly form the basis of a rejection under 35 U.S.C. §102(b) for composition claims 31-32 and 34. Accordingly, Applicants respectfully submit that the rejection must be withdrawn with respect to these claims.

B. Claims 1 and 3 are novel with respect to Knuth *et al.*

Claims 1 and 3 stand rejected under 35 U.S.C. §35 U.S.C. §102(b) as allegedly anticipated by Knuth *et al.* The claims are generally directed to a method for producing vanillin in cultured *Vanilla planifolia*, the method comprising: providing a tissue culture of said *Vanilla planifolia*; and supplementing the culture with a compound selected from the group consisting of malic acid at a concentration of at least about 0.01% by weight of the culture medium, 3,4-dihydroxybenzaldehyde, a combination of malic acid and 3,4-dihydroxybenzaldehyde, and glycosylated lysozyme, in an amount effective to result in the vanillin production in the cultured *Vanilla planifolia*.

As the Office Action correctly asserts, Knuth *et al.* teach a method for producing vanillin in cultured *Vanilla planifolia* cells wherein the culture is supplemented with 10 mg/L malic acid. Knuth *et al.* also teach an increase in the production of vanillin over the course of time from 29 to 47 days of culture form 1.8mg/l to 18mg/l.

Applicants respectfully assert that Knuth *et al.* cannot anticipate applicants claims because Knuth *et al.* teach mail acid at a concentration which is an order of magnitude different from that claimed in the instant invention. Knuth *et al.* only teach malic acid at 10 mg/l, which applicants respectfully assert is one order of magnitude less than the 0.01% (w/v) claimed by Applicants. Applicants note that 0.01% (w/v) is 1 part supplement per 10,000 parts– which is, in fact, an order of magnitude greater than the 10mg/l or 10 parts supplement per million parts (or 1 part supplement per 100,000 parts) taught by Knuth *et al.*

Since the legal standard for anticipation is that each and every limitation must be taught expressly or inherently by the asserted reference, Knuth *et al.* clearly cannot anticipate Applicants' claimed invention. Knuth *et al.* simply does not teach the limitation of malic acid at a concentration of at least 0.01%. Applicants' therefore respectfully assert that the rejection is not proper and must be withdrawn in view of the differences between what is claimed in claims 1 and 3, and what is taught by Knuth *et al.* regarding the concentration of the supplement. Accordingly, Applicants' request reconsideration and withdrawal of the rejection.

III. The Claims are Adequately Described and Fully Enabled Under 35 U.S.C. §112, First Paragraph.

A. The Claimed Invention is Adequately Described.

Claims 9-10, 31-32 and 34 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in such a way as to convey to one skilled in the art that the inventors, at the time of filing, had possession of the claimed invention.

The claims are directed to cell cultures comprising *Vanilla planifolia* cells in culture medium supplemented with an elicitor of vanillin synthesis selected from the group

consisting of malic acid, 3,4-dihydroxybenzaldehyde, a combination of malic acid and 3,4-dihydroxybenzaldehyde, and glycosylated lysozyme, wherein, after 15 days in culture, the cell culture produces at least twice or ten times as much vanillin as a cell culture after 15 days in culture under equivalent conditions, in a culture medium which was not supplemented with the elicitor.

The Office Action alleges that the claimed invention lacks written description under the current Written Description Guidelines. The Office Action further alleges the claim is drawn to cultured *Vanilla planifolia* cells whose sole identifying characteristic is the amount of vanillin produced when cultured according to the claimed methods. The Office Action alleges that the amount of vanillin produced when cultured according to the claimed methods is not a sufficient relevant identifying characteristic in and of itself, as the amount of vanillin produced by cultured *Vanilla planifolia* cells is known to be variable.

No reference is cited for the foregoing proposition that the amount of vanillin produced by cultured *Vanilla planifolia* cells is known to be variable. To the extent that the statement in the Office Action regarding the variability of vanillin production is the Examiner's opinion or own knowledge, Applicants' request that supporting references be provided.

To the extent that the statement in the Office Action regarding the variability of vanillin production relies on the previously cited Rao *et al.* reference, to support this otherwise unsupported statement, Applicants' respectfully traverse the rejection. As has been previously acknowledged by the Examiner, none of the compounds recited in the instant claims are cited by Rao *et al.* and that none are even phytohormones. *Official Action dated 6/03/02*, page 7. The Office Action at that time further acknowledged that Rao *et al.* was cited to demonstrate the unpredictability of "different compounds" on the production of vanillin in cultured *Vanilla planifolia* cells. *Id.*

Applicants respectfully assert neither reliance on Rao *et al.* or on a general state of the art is sufficient to meet the Examiner's burden under the Written Description Guidelines. General allegations of "unpredictability in the art" are not sufficient reasons to support a rejection for lack of adequate written description. Written Description Guidelines, *Federal Register*, Vol. 66, No. 4, Jan. 5, 2001, pages 1099-1111. See also MPEP 2163.04(I)(B).

Applicants further respectfully assert these generalizations reveal nothing as to why an ordinarily skilled artisan would not recognize that the inventors were in possession of the claimed invention in view of the specification; thus the generalizations have no bearing on the adequacy of the written description of the instant claims. The skilled artisan would be convinced from the specification that the inventors were in possession of the claimed invention. Accordingly, Applicants respectfully assert that the assertion of unpredictability in the production of vanillin as it relates the claimed invention is unsupported in the record, or is only supported by inadequate generalizations based on Rao *et al.* which do not relate in any way to the predictability of the production of vanillin in accordance with the claimed invention, nor do they relate to the adequacy of the written description. Applicants further assert that the Office has not met its burden of establishing lack of written description, and that the general unpredictability in the art as the sole basis for rejecting the claims for inadequate written description is not proper under the guidelines.

While the Applicants assert that the claimed compositions are adequately described, in the absence of any indicia of unpredictability directly relating to the subject matter of applicants claims, Applicants additionally assert that the Office Action has not set forth any objective reason to doubt the usefulness of the amount of vanillin at day 15 of culture as a further sufficient relevant identifying characteristic of a cell culture composition as claimed. One of skill in the art would recognize that characteristic as distinguishing the claimed subject matter from all other cell cultures. Accordingly, Applicants respectfully request reconsideration of the adequacy of the written description with respect to claims 31-21, and 34, and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

B. The Specification Teaches the Skilled Artisan How to Make and Use the Claimed Invention

Claims 1-7, 9-10, and 31-34 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while admittedly enabling for a method for producing vanillin in cultured *Vanilla planifolia* cells by supplementing the culture with 3% malic acid alone, 1mM 3,4-dihrdoxybenzaldehyde alone, or 30 μg/ml glycosylated lysozyme elicitor protein

alone, allegedly does not reasonably provide enablement for a method for producing vanillin in cultured *Vanilla planifolia* cells by supplementing the culture with other combinations of compounds or other supplements. The Applicants respectfully traverse the rejection and request reconsideration.

The Office Action acknowledges that the particular culture supplementations and combination recited in the claims are set forth in the specification, and the ranges of the amounts of the supplements are also set forth in the specification, the "effect of the particular culture supplementations and combination on vanillin production is not set forth in the specification." Applicants thus respectfully assert that the claims are fully enabled by the entire specification – the examples are not the limit of the teachings of the Applicants disclosure. There is no statutory, or regulatory support for attempting to limit the Applicants to the Examples to the exclusion of all else that is taught in the specification.

The question of enablement is a question of law, based on underlying factual determination. *Amgen, Inc. v. Hoechst Marion Roussel, Inc. et al.*, 314 F.3d 1313,1334 (Fed. Cir. 2003). Before any analysis of enablement can occur, it is necessary for the examiner to construe the claims. The examiner should always look for enabled, allowable subject matter and communicate to Applicants what that subject matter is at the earliest point possible in the prosecution of the application. (MPEP 2164.04)

The Federal Circuit has consistently held that "the specification must teach those of ordinary skill in the art how to make and use the full scope of the invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1561 (Fed. Cir. 1993). The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given the what they already know, the specification teaches those skilled in the art enough that they can make and use the invention without "undue experimentation." *Amgen*, 314 F.3d at 1334. The fact that a quantity of experimentation, even complex experimentation, may be required is not dispositive of the analysis (MPEP 2164.04). The key word is "undue," not "experimentation". *In re Angstadt*, 537 F.2d 498,504 (CCPA 1976). The factors to be considered in determining whether experimentation is undue include the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use

the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). It is improper to conclude that a disclosure is not enabling based on analysis of only one of the factors while ignoring one or more of the others. MPEP 2164.01(a).

Nevertheless, not everything necessary to practice the invention need be disclosed. The Federal Circuit has stated that what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). Further, the scope of enablement must only bear a reasonable connection to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). Additionally, as the Federal Circuit recently reiterated, the law is clear that the specification need teach only one mode of making and using a claimed composition. *Amgen*, 314 F.3d at 1335.

In the instant case, the Office Action has set out subject matter deemed enabling and allowable, and Applicants wish to express their thanks to the Examiner. Applicants respectfully assert the claims are fully enabled, however, particularly in view of the amendments. The claims have been narrowed previously to advance prosecution. Applicants respectfully assert that the claims presently under consideration are fully enabled and the Office Action improperly attempts to require a more exacting standard than is required under 35 U.S.C. §112, first paragraph.

The Office Action is read to require that the effect of each particular concentration within a range be set forth in the specification, and that the effects of this combination specifically be set forth in the specification. As indicated above, this is clearly not the proper standard under the Patent and Trademark practice, nor under Federal Circuit law.

The Office Action cites the reasons stated in the prior Office Action as the basis for the rejection. The Office Action apparently adopts general conclusions based on the post-filing date review article by Rao *et al.* asserted in the prior Office Action and interprets these broad generalizations as clearly establishing unpredictability in the relevant art. For example, the effects of phytohormones on secondary metabolism were apparently deemed relevant because vanillin is a product of secondary metabolism; conclusions based on phytohormones were apparently deemed relevant because phytohormones are routinely employed in the culture of *Vanilla planifolia* cells; and Rao *et al.* is deemed generally relevant because one of the claimed compounds, a compound not even cited by Rao *et al.*, is considered to be an immediate precursor of vanillin. *Official Action dated 6/03/02*, pages 7-8. The prior Office

Action also alleged that unpredictability of a compound or compounds improving vanillin production in cultured cells is a reasonable basis to question the scope of enablement.

Applicants respectfully assert that unpredictability with respect to *the claimed methods and compounds* cannot be generally premised on the unpredictability of *any compound,* regardless of whether it is the subject of the claims. The Examiner's burden is to establish unpredictability of the *claimed* methods or compounds. Applicants respectfully assert that he Office Action has simply failed to carry this burden. Applicants are not varying phytohormone levels, thus there is no reason to assume any unpredictability or variability on any bases relating to altering phytohormones. Further, even assuming a certain level of unpredictability, the proper analysis still requires a full consideration of the *Wands* factors. Here given the high level of skill in the art, the working examples and other teachings in the specification and the routine experimentation and ease with which optimizing simple additions to culture medium can be achieved – especially where there is a simple assay for monitoring the results – one of ordinary skill would be fully enabled to make and use the invention in accordance with the scope of the claims.

The Office Action previously alleged that one of skill in the art would not know how or be guided by the specification and what is known in the art to combine and further suggested that since the individual Examples do not teach all of the combinations, as well as the effects of the those combinations that those of skill in the art could not make and use the combinations. Applicants submit herewith a prior art reference by Yin *et al.* teaching and using, in biological research, incomplete factorial design and response surface methods for experimental design. (Yin, Y. and C.W. Carter, Jr., *Nucleic Acids Research* 24: 1279-86, 1996.) Such statistical-based experimental designs are routine in the biological sciences. Applicants respectfully assert that one of skill in the art, armed with the high level of knowledge in the art, and with Applicants specifications could make and use the claimed invention. Applicants did not and need not teach what is well-known in the art – such as basic experimental design. Such experimentation as might be required to optimize a particular combination with the well-defined ranges of elicitors is only routine. A requirement for routine experimentation cannot cause a specification to fail to satisfy the requirements of 35 U.S.C. §112, first paragraph.

Applicants respectfully submit that a full analysis of the *Wands* factors, including the need, if any for routine experimentation, in view of the specification as a whole, requires a finding that the specification is enabling for the claimed invention. Applicants thus respectfully request full reconsideration and withdraw of the rejection under 35 U.S.C. §112, first paragraph.

In view of the foregoing, Applicants respectfully submit that the claims are in order for allowance. An early and favorable reply to that effect is earnestly sought. The Applicants' undersigned representative invites the Examiner to call him at 215-557-5986 to resolve outstanding issues, if any.

Respectfully submitted,

Date: May 27, 2003

Scott E. Scioli
Registration No. 47,930

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439